Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently amended) A compound of formula I:

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof;

wherein independently,

 R_1 and R_2 are: H, lower alkyl, cyclic alkyl, or benzyl;

Y is -[CR₈R₉]_n-, where R₈ is H, and R₉ is aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy, and n is 1.

Y and Z is are: -[C(R)₂]_n-, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

 R_3 , R_4 , R_5 , and R_7 are: H, I, Br, Cl, F, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OR, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

X is: O, S, SO, SO₂, NR, $C(R)_2$, –lower alkyl-O-, -O-lower alkyl-, $COCH_2O$, or OCH_2CO ; and

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy;

PATENT

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

n is 1 to 6; and

provided that the compound is not thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine.

- 2. (original) The compound of claim 1, wherein R₄ and R₅ are H, CH₃, CF₃, CN, OCH₃, CH₂CH₃, or CH(CH₃)₂.
- 3. (original) The compound of claim 2, wherein R_1 and R_2 are H, R_3 is I, R_4 , R_5 , and R_7 are H, R_6 is OH, X is O, Y and Z are each CH₂.
- 4. (original) The compound of claim 1, wherein R₄ is H, CH₃, CF₃, CN, OCH₃, CH₂CH₃, or CH(CH₃)₂; and R₅ is I, Br, Cl, or F.
- 5. (original) The compound of claim 4, wherein R_1 and R_2 are H, R_4 and R_7 are H, R_3 and R_5 is I, R_6 is OH, X is O, Y and Z are each CH₂.
- 6. (original) The compound of claim 4, wherein R_1 and R_2 are H, R_4 is H, R_3 , R_5 , and R_7 are I, R_6 is OH, X is O, Y and Z are each CH₂.
- 7. (original) The compound of claim 1, wherein R_1 is lower alkyl, R_6 is OH or OR, and X is O.
- 8. (original) The compound of claim 1, wherein R_3 is a halogen, R_6 is H, and X is O.
- 9. (original) The compound of claim 1, wherein X is alkoxy.
- 10. (original) The compound of claim 1, wherein R_1 and R_2 are H or lower alkyl, R_6 is H or CF_3 , and X is alkoxy.
- 11. (original) The compound of claim 1, wherein R_1 is H or lower alkyl, and Y is $C(R)_2$.
- 12. (original) The compound of claim 1, wherein R_1 and R_2 are H or lower alkyl, R_6 is H, X is O, Y is O, and Z is alkyl.

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

13. (original) The compound of claim 1, wherein Y is $-[C(R)_2]_n$ -, where R is aryl and n is 1.

14. (Currently amended) A compound of formula II:

$$R_6$$
 R_5
 R_4
 R_8
 R_1
 R_2
 R_5
 R_3

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof;

wherein independently,

R₁ and R₂ are: H, lower alkyl, cyclic alkyl, or benzyl;

Y and Z are: $-[C(R)_2]_{\Pi^-}$, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

 R_3 , R_4 , R_5 , and R_7 are: H, I, Br, Cl, F, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OR, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

R₈ is: OR, R, CH₂OR, CH₂NR₂, CH₂N⁺R₃, CH₂N+R₃, SR, CH₂SR, or lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy

X is: O, S, SO, SO₂, NR, C(R)₂, –lower alkyl-O-, -O-lower alkyl-, COCH₂O, or OCH₂CO;

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; and

n is 1 to 6; and

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

provided that the compound is not thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine.

- 15. (Currently amended) The compound of claim 14 wherein R_8 is $\frac{\text{H-or}}{\text{OCH}_3}$, Y is CONH, and Z is alkyl.
- 16. (original) A compound of formula III:

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form therof;

wherein independently,

 R_1 and R_2 are: H, lower alkyl, cyclic alkyl, or benzyl;

Y and Z are: $-[C(R)_2]_n$ -, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

R₃, R₄, and R₅ are: I, Br, Cl, F, H, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OH, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

 R_7 is: OR, R, CH₂OR, CH₂NR₂, CH₂N[†]R₃, SR, or CH₂SR;

X is: O, S, SO, SO₂, NR, $C(R)_2$, –lower alkyl-O-, -O-lower alkyl-, COCH₂O, or OCH₂CO;

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; and

n is 1 to 6.

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

17. (original) The compound of claim 16, wherein X is O.

18. (Currently amended) A compound of formula IV:

$$R_{6}$$
 R_{7}
 R_{4}
 R_{8}
 $Y-Z-N$
 R_{2}

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form therof;

wherein independently,

 R_1 and R_2 are: H, lower alkyl, cyclic alkyl, or benzyl;

Y and Z are: $-[C(R)_2]_n$ -, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

R₃, R₄, R₅, and R₇ are: I, Br, Cl, F, H, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OH, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

 R_8 is: OR, R, CH₂OR, CH₂NR₂, CH₂N⁺R₃, CH₂N+R₃, SR, CH₂SR

X is: O, S, SO, SO₂, NR, $C(R)_2$, –lower alkyl-O-, -O-lower alkyl-, COCH₂O, or OCH₂CO;

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; and

n is 1 to 6.

- 19. (original) The compound of claim 18, wherein R_1 and R_2 are H or lower alkyl, R_6 is H, X is O, Y is O, and Z is alkyl.
- 20. (original) The compound of claim 18, wherein Y is -CHR- where R is aryl.

Application No.: 10/825,881 Office Action Dated: May 22, 2006

21. (original) A compound of formula V:

$$R_7$$
 R_6
 R_4
 R_5
 R_4
 R_7
 R_2
 R_6

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof;

wherein independently,

R₁ and R₂ are: H, lower alkyl, cyclic alkyl, or benzyl;

Y and Z are: $-[C(R)_2]_n$ -, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

 R_3 , R_4 , R_5 , and R_7 are: H, I, Br, Cl, F, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OR, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

X is: O, S, SO, SO₂, NR, $C(R)_2$, –lower alkyl-O-, -O-lower alkyl-, COCH₂O, or OCH₂CO;

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; and

n is 1 to 6.

22. (original) A pharmaceutical composition, comprising at least one pharmaceutically acceptable carrier or excipient and at least one compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine to the subject.

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

23. (withdrawn) A method of exerting a positive inotropic effect on the heart without affecting the heart rate of a mammalian subject comprising the step of administering to said subject an effective amount of the compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine.

- 24. (withdrawn) A method of exerting a negative inotropic effect on the heart without affecting the heart rate of a mammalian subject comprising the step of administering to said subject an effective amount of an antagonist of the compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine.
- 25. (withdrawn) A method of lowering the core body temperature of a mammalian subject comprising the step of administering to said subject an effective amount of the compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine.
- 26. (withdrawn) The method of claim 9, wherein administering the compound of claim 1 induces torpor or hibernation in said subject.
- 27. (withdrawn) A method of treating a mammalian subject during surgery comprising administering to the subject a therapeutically effective amount of the compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine, or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof.

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

28. (withdrawn) The method of claim 27, wherein said method reduces the core body temperature and induces anesthesia in the subject.

- 29. (withdrawn) The method of claim 27, said method reduces blood loss of the subject.
- 30. (withdrawn) A method for alleviating a disease state in a mammal believed to be responsive to treatment with a thyronamine agonist comprising the step of administering to the mammal a therapeutic amount of the compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine, or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof.
- 31. (withdrawn) The method of claim 30, wherein said composition is an agonist of a G protein coupled receptor.
- 32. (withdrawn) The method of claim 31, wherein said composition is an agonist of a trace amine receptor.
- 33. (withdrawn) The method of claim 30, wherein the disease state is congestive heart failure.
- 34. (withdrawn) The method of claim 30, wherein the disease state is fever or heatstroke.
- 35. (withdrawn) The method of claim 30, wherein the disease state is bipolar disorder, depression, schizophrenia, eating disorders, anxiety, seizure, epilepsy, insomnia and sleeping disorders, gastro esophageal reflux disease, diseases involving gastrointestinal motility or asthma.
- 36. (withdrawn) The method of claim 30, wherein the disease state is diabetes, hyperglycemia, hypoglycemia, cardiac arrhythmia, stroke, osteoporosis, obesity, atherosclerosis, hypertension, hyperthyroidism or hypothyroidism.

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

37. (withdrawn) A method for alleviating a disease state in a mammal believed to be responsive to treatment with a thyronamine antagonist comprising the step of administering to the mammal a therapeutic amount of the compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine, or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof.

- 38. (withdrawn) The method of claim 37, wherein said composition is an antagonist of a G protein coupled receptor.
- 39. (withdrawn) The method of claim 38, wherein said composition is an antagonist of a trace amine receptor.
- 40. (withdrawn) The method of claim 37, wherein the disease state is congestive heart failure.
- 41. (withdrawn) The method of claim 37, wherein the disease state is fever or heatstroke.
- 42. (withdrawn) The method of claim 37, wherein the disease state is bipolar disorder, depression, schizophrenia, eating disorders, anxiety, seizure, epilepsy, insomnia and sleeping disorders, gastro esophageal reflux disease, diseases involving gastrointestinal motility or asthma.
- 43. (withdrawn) The method of claim 37, wherein the disease state is diabetes, hyperglycemia, hypoglycemia, cardiac arrhythmia, stroke, osteoporosis, obesity, atherosclerosis, hypertension, hyperthyroidism or hypothyroidism.
- 44. (withdrawn) A method of treating a mammalian subject during open heart surgery believed to be responsive to treatment with a thyronamine antagonist comprising administering a therapeutically effective amount the compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine,

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine, or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof, to the subject.

- 45. (withdrawn) A method of treating a mammalian subject during trauma or blood loss believed to be responsive to treatment with a thyronamine antagonist comprising administering a therapeutically effective amount the compound of claim 1, claim 14, claim 16, claim 18, or claim 21, or thyronamine, 3,5-diiodothyronamine, 3,5,3'-triiodothyronamine, thyroxamine, 3,5,3',5'-tetraiodothyroethanolamine, 3,5,3'-triiodothyroethanolamine, or 3,5-diiodothyroethanolamine, or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof, to the subject.
- 46. (Currently amended) An isotopically labeled compound of claims claim 1, claim 14, claim 16, claim 18, or claim 21.
- 47. (original) The compound of claim 46 isotopically labeled with ³H, ²H, or ¹²⁵I.
- 48. (withdrawn) An antibody that specifically binds to the compound of claim 1, claim 14, claim 16, claim 18, or claim 21.
- 49. (withdrawn) A method for preparing a protected phenylboronic acid, comprising the steps of:

providing a protected *p*-bromophenol; and reacting said protected *p*-bromophenol with alkyl lithium and B(OR)₃; and hydrolyzing the product of said reacting step to form a protected phenylboronic acid, where R is methyl, ethyl or propyl.

50. (withdrawn) A method according to claim 49, wherein said protected *p*-bromophenol is protected with a moiety selected from trimethylsilyl, *tert*-butyldimethylsilyl, triisopropylsilyl and methoxymethylether.

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

51. (withdrawn) A method for preparing a thyronamine derivative, comprising the steps of:

contacting, in the presence of copper, an amino-protected tyramine of the formula:

$$R_3$$
 PG
 PG
 PG
 PG

with a hydroxyl- or thiol-protected phenylboronic acid of the formula:

$$R_7$$
 $PG)_{\overline{OH/SH}}$
 Q
 R_5

to form the structure of the formula:

$$R_7$$
 R_3
 Y
 Z
 NH_2

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof;

deprotecting said hydroxyl or thiol group; and

deprotecting said amino group;

wherein,

(PG)_a is an amino protecting group;

(PG)_{OH/SH} is a hydroxyl- or thiol-protecting group;

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

Q is: O or S;

Y and Z are: $-[C(R)_2]_{n}$ -, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

 R_3 , R_4 , R_5 , and R_7 are: H, I, Br, Cl, F, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OR, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

X is: O, S, SO, SO₂, NR, $C(R)_2$, –lower alkyl-O-, -O-lower alkyl-, COCH₂O, or OCH₂CO; and

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy;

n is 1 to 6.

- 52. (withdrawn) A method according to claim 51, further comprising the step of independently substituting an I, Br, Cl or F at the 3' position, 5' position or both the 3' position and the 5' position.
- 53. (withdrawn) A method according to claim 51, further comprising the step of Oalkylating or S-alkylating the hydroxyl or thiol functionality of said compound.
- 54. (withdrawn) A method according to claim 51, further comprising the step of N-alkylating the amino functionality of said compound.
- 55. (withdrawn) A method for preparing a thyronamine derivative, comprising the steps of:

contacting, in the presence of copper, an amino-protected tyramine of the formula:

$$R_{3}$$
 R_{4}
 R_{8}
 Y
 Z
 N
 $(PG)_{a}$

Page 13 of 22

Application No.: 10/825,881 Office Action Dated: May 22, 2006

with a hydroxyl- or thiol-protected phenylboronic acid of the formula:

$$R_7$$
 $PG)_{\overline{OH/SH}}$
 R_5

to form the structure of the formula:

$$R_{6}$$
 R_{5}
 R_{4}
 R_{8}
 R_{8}
 $Y-Z-N$
 H

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof;

deprotecting said hydroxyl or thiol group; and

deprotecting said amino group;

wherein,

(PG)_a is an amino protecting group;

(PG)_{OH/SH} is a hydroxyl- or thiol-protecting group;

Q is: O or S;

Y and Z are: $-[C(R)_2]_n$ -, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

 R_3 , R_4 , R_5 , and R_7 are: H, I, Br, Cl, F, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OR, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

R₈ is: OR, R, CH₂OR, CH₂NR₂, CH₂N+R₃, SR, CH₂SR;

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

X is: O, S, SO, SO₂, NR, C(R)₂, –lower alkyl-O-, -O-lower alkyl-, COCH₂O, or OCH₂CO;

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; and

n is 1 to 6.

56. (withdrawn) A method for preparing a thyronamine derivative, comprising the steps of:

contacting, in the presence of copper, an amino-protected tyramine of the formula:

$$R_3$$
 R_7
 Y
 Z
 N
 R_7
 $(PG)_a$

with a hydroxyl- or thiol-protected phenylboronic acid of the formula:

$$R_5$$
 OH R_5 OH R_4 R_4

to form the structure of the formula:

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof;

PATENT

deprotecting said hydroxyl or thiol group; and

deprotecting said amino group;

wherein,

(PG)_a is an amino protecting group;

(PG)_{OH/SH} is a hydroxyl- or thiol-protecting group;

Q is: O or S;

Y and Z are: $-[C(R)_2]_n$ -, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

R₃, R₄, and R₅ are: I, Br, Cl, F, H, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OH, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

R₇ is: OR, R, CH₂OR, CH₂NR₂, CH₂N⁺R₃, SR, or CH₂SR;

X is: O, S, SO, SO₂, NR, $C(R)_2$, –lower alkyl-O-, -O-lower alkyl-, COCH₂O, or OCH₂CO;

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; and

n is 1 to 6.

57. (withdrawn) A method for preparing a thyronamine derivative, comprising the steps of:

contacting, in the presence of copper, an amino-protected tyramine of the formula:

$$R_4$$
 R_8
 Y
 Z
 N
 $(PG)_a$

with a hydroxyl- or thiol-protected phenylboronic acid of the formula:

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

$$R_7$$
 $PG)_{\overline{OH/SH}}$
 Q
 R_5

to form the structure of the formula:

$$R_{6}$$
 R_{7}
 R_{4}
 R_{8}
 $Y-Z-N$
 R_{3}
 R_{4}
 R_{5}
 R_{4}
 R_{5}
 R_{4}
 R_{5}
 R_{4}
 R_{5}
 R_{4}
 R_{5}
 R_{6}
 R_{7}
 R_{8}
 R_{8}
 R_{8}
 R_{8}
 R_{1}
 R_{1}
 R_{2}
 R_{3}

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof;

deprotecting said hydroxyl or thiol group; and

deprotecting said amino group;

wherein,

(PG)_a is an amino protecting group;

(PG)_{OH/SH} is a hydroxyl- or thiol-protecting group;

Q is: O or S;

Y and Z are: $-[C(R)_2]_{n}$, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

 R_3 , R_4 , R_5 , and R_7 are: I, Br, Cl, F, H, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OH, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

R₈ is: OR, R, CH₂OR, CH₂NR₂, CH₂N+R₃, SR, CH₂SR

X is: O, S, SO, SO₂, NR, $C(R)_2$, –lower alkyl-O-, -O-lower alkyl-, $COCH_2O$, or OCH_2CO ;

Application No.: 10/825,881 **Office Action Dated:** May 22, 2006

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; and

n is 1 to 6.

58. (withdrawn) A method for preparing a thyronamine derivative, comprising the steps of:

contacting, in the presence of copper, an amino-protected tyramine of the formula:

$$R_3$$
 Y Z N $(PG)_a$

with a hydroxyl- or thiol-protected phenylboronic acid of the formula:

to form the structure of the formula:

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof;

deprotecting said hydroxyl or thiol group; and

Application No.: 10/825,881 Office Action Dated: May 22, 2006

deprotecting said amino group;

wherein,

(PG)_a is an amino protecting group;

(PG)_{OH/SH} is a hydroxyl- or thiol-protecting group;

Q is: O or S;

Y and Z are: $-[C(R)_2]_{\Pi}$ -, CHOR, O, S, NR, CONH, or NHCO, provided that Y and Z are not both O, both S, both NR, both CONH, both NHCO, or CONH and NHCO;

 R_3 , R_4 , R_5 , and R_7 are: H, I, Br, Cl, F, CH₃, CF₃, CN, SR, OCH₃, CH₂CH₃, or CH(CH₃)₂;

 R_6 is: OR, H, SH, F, CF₃, lower alkyl, or $N(R)_2$;

X is: O, S, SO, SO₂, NR, $C(R)_2$, –lower alkyl-O-, -O-lower alkyl-, COCH₂O, or OCH₂CO;

R is H, lower alkyl, aryl optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; or benzyl wherein said phenyl portion is optionally substituted with 1-3 substituents selected from the group consisting of lower alkyl, halo, hydroxy, and alkoxy; and

n is 1 to 6.

- 59. (New) The compound of claim 1, wherein R₉ is benzyl wherein said phenyl portion is substituted with hydroxyl.
- 60. (New) The compound of claim 59 wherein, R_1 , R_2 , R_3 , R_5 , and R_7 are H, R_4 is I, R_6 is hydroxyl, X is O, and Z is CH_2 .